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| 09 923,870 | 08 06 2001 | Bernhard Palsson | PALSSN.002C1 | 1729 |

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EXAMINER

ALLEN, MARIANNE P

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| ART UNIT | PAPER NUMBER |
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1631

DATE MAILED: 11 20 2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/923,870

Applicant(s)

PALSSON, BERNHARD

Examiner

Marianne P. Allen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 6) ☐ Other: _____

DETAILED ACTION

Claims 1-23 are under consideration by the examiner.

Information Disclosure Statement

The Gallperin et al. reference could not be considered as it was not present in the parent application. This reference has been lined through on the Form PTO-1449.

Oath/Declaration

This application presents a claim for subject matter not originally claimed or embraced in the statement of the invention. A supplemental oath or declaration is required under 37 CFR 1.67. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Applicant's transmittal papers state that the instant application is a continuation of parent application 09/243,022. This is not correct. The present application is a continuation-in-part of 09/243,022. It is noted that the claims originally filed with this application are not the same as those originally filed in parent application 09/243,022. These claims could not have been introduced into the parent application without a rejection with respect to new matter. The steps and computer system elements as presently claimed have no support in the specification as filed. As such, a new CIP oath is required. Note that in view of the above remarks applicant is entitled to only the instant filing date of 8/6/01 and not the filing date of parent application 09/243,022. Should applicant believe otherwise, they are invited to point out by page and line number basis for each and every limitation (step) in the specification as recited in the claims.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The method for determining a phenotype of an organism with the recited steps and preamble goal and the computer system with the recited elements (including the limitations of the dependent claims) are not disclosed in the specification.

Claim 16 is objected to because of the following informalities: Claim 16 has two terminal periods (“.”). Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See at least page 14.

Also, the specification refers to item “50” in Figure 2 on at least page 9, line 25; page 10, line 10; and page 10, line 22. However, item 50 is not found in any of the figures.

Claim Rejections - 35 USC § 112

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Claim 1 is directed to a method for determining a phenotype of an organism and claim 12 is directed to a computer system comprising a memory having instructions that when executed perform the steps of the method.

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The specification does not make clear what must be done to achieve “determining a phenotype.” That is, it is not known what a phenotype of an organism within the context of the claims is. Note that the final step of “determining a phenotype of the organism by performing a mathematical analysis of the table of metabolic reactions” doesn’t specify the type of mathematical analysis performed nor how the determination is made. The examiner has reviewed the specification and prior art carefully. While the specification discusses a metabolic phenotype on page 11 (note the claims are not limited to a **metabolic** phenotype), the method steps and computer system as claimed for the determination are not disclosed. In the prior art Varma et al. defines a metabolic phenotype as the optimal flux distribution for a particular assumed behavior (such as maximal growth rates) calculated using linear optimization. However, the claims do not reflect the definition of Varma et al. as none of the claims require determination of the optimal flux distribution for a particular assumed behavior calculated using linear optimization. Furthermore, the disclosure on page 11 is not the same as the disclosure of Varma et al. The specification states, “The particular utilization of the metabolic genotype can be defined as the *metabolic phenotype* that is expressed under those particular conditions.” This is not a clear definition of a “determining a phenotype” and does not clearly set forth what is to be determined or how. Even if it were, the claims do not reflect the mathematic optimization equations disclosed with reference to a metabolic phenotype on page 11. No other disclosure with respect to metabolic phenotypes appears to be present in the specification.

The claims require a table of metabolic reactions known to take place in the organism wherein the products of at least one metabolic reaction are linked to the reactants of another metabolic reaction. These reactions and the pathways to which they belong are not known for a

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large number of organisms. In many cases, knowledge of an enzyme present in an organism does not provide any information as to how this enzyme fits into the metabolic network. As such, one would be required to determine and develop such a table for the organism of interest. This constitutes undue experimentation as there is no guidance on developing such a table.

In addition, the specification does not provide guidance on how assignment of function would then provide the metabolic reaction of the candidate metabolic gene. That is, assigning the function of a kinase based upon homology does not provide the substrate and product of the reaction.

Claims 2-8, 11, 14-20, and 23 appear to be directed to a method of designing a table of metabolic reactions such that when a flux balance methodology is applied gives a particular result. (See rejection under 112, 2nd paragraph, below.) If these claims are intended to be a stated objective driving the flux balance model, the claims do not reflect this and the specification does not provide guidance to design organisms (*in silico* organisms if fewer than all metabolic reactions for the actual organism are included?) of a particular phenotype. It is unclear how to execute a method where candidate metabolic genes are added and unknown metabolic genes are removed. Are steps of the method executed multiple times (which the claims do not specify)? If multiple iterations are required, when does the method terminate and under what conditions?

Finally, the specification lacks guidance in setting forth reasonable means for assigning a function based on a homology comparison. With regards to gene assignment based on homology, the specification does not teach the specific computational guidelines for identifying the gene function of the target based on those of known function. Applicant describes the

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generic process for assigning function based on homology (i.e., using BLAST and FAST), however, the factors determining how one of skill in the art would select the appropriate homologues is not disclosed (i.e., selection criteria for functional assignment). For example: 1) what is the cutoff for percent homology before assigning a function; 2) what regions of the gene expression product weight the highest during a selection; 3) how one should account for shifts in residues; 4) what to do if the results of the homology match to metabolic genes with different functions; and/or 5) what to do if no matches are provided. In addition, the prior is unpredictable with respect to the functional assignment of unknown gene based on a homology comparison. The prior art has demonstrated that assignment of a metabolic gene to a know function based on homology comparisons provide improper functional assignment (see the homology-based methods of functional assignment of Everett et al., *Nature Genetics* 17, 411-422, 1997 in light of the experimental conclusions of Scott et al., *Nature Genetics* 21, 440-443, 1999). Everett et al. disclose a homology-based functional assignment to a putative, mutated sulfate transporter gene (PDS; which encodes "pendrin") identified through positional cloning in Pendred syndrome populations. The homology-based searches were carried out using BLAST and PSI-BLAST with commercial databases using human pendrin as the query sequence. The conclusions of Everett et al. based upon the homology comparisons were that pendrin was a transporter of sulfate. However, experimental studies by Scott et al., clearly demonstrate that pendrin, which has: 1) 29% homology to the rat sulfate-ion transporter encoded by *Sat-1*; 2) 32% homology to the human diastrophic dysplasia sulfate transporter *DTD*; and 3) 45% homology to the human sulfate transporter downregulated in adenoma encoded by *DRA*, is not a transporter of sulfate, but of chloride and iodine.

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Claims 2-8, 11, 14-20, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 14 are confusing in requiring an additional step that does not clearly further limit the method. The claims do not indicate where within the method of the independent claim the additional step occurs. In addition, they appear to specify the phenotype that is supposed to be determined by the method of the independent claim. That is, it appears that the claim is no longer directed to determining a phenotype but rather is directed to a method of designing a table of metabolic reactions such that when a flux balance methodology is applied gives a particular result, for example. If the outcome (particular phenotype) is specified in the claim, how can the method determine it? Claims 3-8, 11, 15-20, and 23 are likewise confusing.

It is not known what phenotype meets the limitations of "suboptimal." Suboptimal for what?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Edwards et al. (Journal of Biological Chemistry, June 1999).

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Applicant is entitled to only the instant filing date of 8/6/01 and not the filing date of parent application 09/243,022 for the reasons set forth above. Again, should applicant believe otherwise, they are invited to point out by page and line number basis for each and every limitation (step) in the parent specification as recited in the claims.

Edwards et al. discloses determining six optimal phenotypes from the same metabolic genotype using different constraining features for *Haemophilus influenzae* Rd. Some metabolic genes used in the analysis had function assigned based upon homology to known genes. Flux balance analysis was used with linear programming. See abstract and materials and methods. Conditions for optimal growth and minimal media were determined. See results and Figure 2. Effects of gene deletions, including lethal deletions, are shown. See Figure 3. With respect to claim 13, the reference does not specify the particular type of memory used but given the nature of the computation, at least one of the listed memories must have been used to execute the method.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 703-308-0666. The examiner can normally be reached on Monday-Friday, 8:30 am - 2:30 pm.

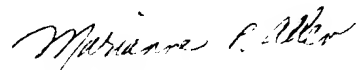
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703-308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Marianne P. Allen
Primary Examiner
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mpa

November 19, 2002